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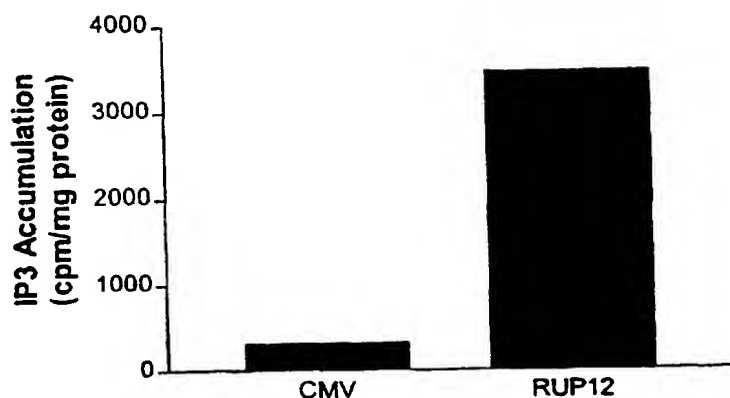
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[Continued on next page]

(54) Title: ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

IP3 Assay in 293 Cells



(57) Abstract: The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/31509

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K14/705 C12N15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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EPO-Internal, EMBL, STRAND, WPI Data, EMBASE, CHEM ABS Data, MEDLINE, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 46620 A (MILLENNIUM PHARM INC) 22 October 1998 (1998-10-22) claim 1; figures 1A, 2A; example 8	1-4
X	US 5 891 720 A (WOOLF ELIZABETH A ET AL) 6 April 1999 (1999-04-06) Sequence No. 2 abstract	1-4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STADEL J M ET AL: "Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 18, no. 11, 1 November 1997 (1997-11-01), pages 430-437, XP004099345 ISSN: 0165-6147 abstract; table 1 ---	1-4
A	KJELSBORG M A ET AL: "Constitutive activation of the alpha1B-adrenergic receptor by all amino acid substitutions at a single site" JOURNAL OF BIOLOGICAL CHEMISTRY,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD,US, vol. 267, no. 3, 25 January 1992 (1992-01-25), pages 1430-1433, XP002135768 ISSN: 0021-9258 abstract ---	1-4
A	O'DOWD B F ET AL: "DISCOVERY OF THREE NOVEL G-PROTEIN-COUPLED RECEPTOR GENES" GENOMICS,ACADEMIC PRESS, SAN DIEGO,US, vol. 47, no. 2, 15 January 1998 (1998-01-15), pages 310-313, XP000863786 ISSN: 0888-7543 abstract ---	1-4
A	WO 97 21731 A (NEW ENGLAND MEDICAL CENTER INC) 19 June 1997 (1997-06-19) page 18, line 18-26; figures 2,3 ---	1-4 -
A	MARCHESE A ET AL: "Novel GPCRs and their endogenous ligands: expanding the boundaries of physiology and pharmacology" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 20, no. 9, 1 September 1999 (1999-09-01), pages 370-375, XP004178194 ISSN: 0165-6147 abstract --- -/--	1-4

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Inter. Patent Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>DATABASE EMBL 'Online! Accession Nr. Q9NTT0, 1 October 2000 (2000-10-01) COLLIER R.: "DJ680N.3 (G-Protein Coupled Receptors) (Fragment)" XP002168498 abstract</p>	1-4
P, X	<p>WO 00 22131 A (ARENA PHARMACEUTICALS INC ;GORE MARTIN (US); LIAW CHEN W (US); LIN) 20 April 2000 (2000-04-20) the whole document</p>	1-4
X	<p>DATABASE EMBL 'Online! AC: AC008728, 4 August 1999 (1999-08-04) DOE JOINT GENOME INSTITUTE: "Sequencing of Human Chromosome 5" XP002175776 abstract</p>	5-8
A	<p>WO 98 29439 A (SULLIVAN KATHLEEN ;MERCK & CO INC (US); TAN CARINA (US)) 9 July 1998 (1998-07-09) page 57; figure 13; example 14</p>	5-8
E	<p>WO 01 14577 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US)) 1 March 2001 (2001-03-01) page 30-31; claims 1,2</p>	5-8
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>DATABASE EMBL 'Online! AC: AB038237, 4 May 2000 (2000-05-04) OHONO ET AL.: "Homo sapiens mRNA for G proteine-coupled receptor C5L2, complete cds" XP002175947 abstract</p>	9-12
P, X	<p>WO 00 14229 A (ONO MITSU HARU ;KANNO KIMIYOSHI (JP); ASAHI CHEMICAL IND (JP); ISHI) 16 March 2000 (2000-03-16) page 98 -page 101; claim 4 page 103; claim 5</p>	9-12
E	<p>WO 01 36471 A (ARENA PHARMACEUTICALS INC ;CHEN RUOPING (US); DANG HUONG T (US); L) 25 May 2001 (2001-05-25) Seq. Id. No. 3 (claims 5-8) Seq. Id. No. 5 (claims 9-12) Seq. Id. No. 7 (claims 13-16) Seq. Id. No. 9 (claims 17-20) Seq. Id. No. 11 (claims 17-20) Seq. Id. No. 13 (claims 25-28) Seq. Id. No. 21 (claims 41-44) Seq. Id. No. 19, 23 (claims 45-48) Seq. ID. No. 25 (claims 49-52)</p>	5-28, 41-52
E	<p>EP 1 094 076 A (PFIZER LTD ;PFIZER (US)) 25 April 2001 (2001-04-25) Seq. Id. No. 1</p>	9-12
E	<p>WO 01 31014 A (UPJOHN CO ;VOGELI GABRIEL (US); WOOD LINDA S (US); MERCHANT KALPAN) 3 May 2001 (2001-05-03) Sequence No. 5</p>	13-16
X	<p>PATENT ABSTRACTS OF JAPAN vol. 1999, no. 09, 30 July 1999 (1999-07-30) & JP 11 098988 A (SMITHKLINE BEECHAM CORP), 13 April 1999 (1999-04-13) abstract & DATABASE EMBL 'Online! AC: E31720; E75225, 22 February 2001 (2001-02-22) JEFFREY L.M.D.D. AND BERGSUMA W.S.H.H.: "cDNA clone HeoAd54 encoding human seven-pass transmembrane receptor" abstract</p>	13-16
X	<p>US 5 955 308 A (BERGSMA DERK J ET AL) 21 September 1999 (1999-09-21) Sequence 1</p>	13-16

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INTERNATIONAL SEARCH REPORT

Inte. .onal Application No

PCT/US 00/31509

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 892 051 A (SMITHKLINE BEECHAM CORP) 20 January 1999 (1999-01-20) page 20 -page 21; claim 11 ---	13-16
X,P	DATABASE EMBL 'Online! AC: AP000808, 3 December 1999 (1999-12-03) HATTORI M. ET AL.: "Homo sapiens 171,539 genomic of 11q13" XP002175780 abstract ---	17-20
X	WO 99 32519 A (FORTIN YVES ;LEMBO PAOLA (CA); AHMAD SULTAN (CA); BANVILLE DENIS () 1 July 1999 (1999-07-01) page 48 -page 54; claims 16,20,21 ---	37-40
A	page 55 -page 56; claim 25 page 52 -page 54; claim 21 ---	17-20, 57-60 37-40 37-40
X	DATABASE EMBL 'Online! AC011780 , 18 October 1999 (1999-10-18) BIRREN B., LINTON L., NUSBAUM C., LANDER E.: "Homo sapiens clone RP11-15H8, 31 unordered pieces." XP002175781 abstract ---	21-24
X	JP 08 245697 A (TAKEDA CHEM IND LTD) 24 September 1996 (1996-09-24) claim 4; figures 1,2 ---	21-24
X	WO 96 05302 A (FUJII RYO ;HOSOYA MASAKI (JP); OHGI KAZUHIRO (JP); FUKUSUMI SHOJI) 22 February 1996 (1996-02-22) page 263 -page 264; example 16 ---	21-24
P,X	DATABASE EMBL 'Online! AC: AL355310 , 5 May 2000 (2000-05-05) WALLIS, J: "Human DNA sequence from clone RP5-1160K1" XP002175782 abstract ---	21-24
X	DATABASE EMBL 'Online! AC: A0001459, ADAMS M.D. ET AL. : "CIT-HSP-2286K19.TF CIT-HSP Homo sapiens genomic clone 2286K19, genomic survey sequence" XP002175783 abstract ---	25-28
A	EP 0 878 542 A (SMITHKLINE BEECHAM CORP) 18 November 1998 (1998-11-18) page 18 -page 19; claim 1 ---	25-28
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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/31509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HEISE CHRISTOPHER E ET AL: "Characterization of the human cysteinyl leukotriene 2 receptor." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 39, 29 September 2000 (2000-09-29), pages 30531-30536, XP002175775 ISSN: 0021-9258 the whole document & DATABASE EMBL 'Online! AC: AF254664, HEISE C.E. ET AL.: "Homo sapiens cysteinyl leukotriene receptor CYSLT2 gene, complete cds." abstract	25-28
A	US 5 861 309 A (WEINSHANK RICHARD L ET AL) 19 January 1999 (1999-01-19) Sequence 1	29-32
E	WO 01 09184 A (DELEERSNIJDER WILLY ;NYS GUY (BE); ZHANG FAN (BE); SOLVAY PHARMACE) 8 February 2001 (2001-02-08) Sequence 1 page 6 -page 7; claims 1,15	29-32
P,X	DATABASE EMBL 'Online! AC016462, 1 December 1999 (1999-12-01) BIRREN B. ET AL. : " Homo sapiens clone RP11-14N15" XP002175784 abstract	29-32
A	WO 99 48921 A (ORGANON NV ;SPEK PETRUS JOHANNES V D (NL); UNIV LELAND STANFORD JU) 30 September 1999 (1999-09-30) claims 2,4; figure 4	33-36 -
P,X	DATABASE EMBL 'Online! AL136106, 7 January 2000 (2000-01-07) BURTON J: "Human DNA sequence from clone RP11-15909" XP002175785 abstract	33-36
X	DATABASE EMBL 'Online! AC: AC008547, OE JOINT GENOME INSTITUTE STANFORD HUMAN GENOME CENTER.: "Homo sapiens chromosome 5 clone CTC-502M5, complete sequence." XP002175786 abstract	41-44

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INTERNATIONAL SEARCH REPORT

Inte .onal Application No

PCT/US 00/31509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 06552 A (GENSET SA ;LACROIX BRUNO (FR); DUCLERT AYMERIC (FR); DUMAS MILNE E) 11 February 1999 (1999-02-11) SEQ ID NO: 95	41-44
A	EP 0 612 845 A (AMERICAN CYANAMID CO) 31 August 1994 (1994-08-31) claim 2; figure 9	49-52
A	DATABASE EMBL 'Online! AC: AL065769, 29 May 1999 (1999-05-29) GEMPSCPUE: "Drosophila melanogaster genome survey sequence TET3 end of BAC # BACR08K10 of RPCI-98 library from Drosophila melanogaster (fruit fly)" XP002175910 abstract	49-52
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A	BOYER JOSE L ET AL: "Molecular cloning and expression of an avian G protein-coupled P2Y receptor." MOLECULAR PHARMACOLOGY, vol. 52, no. 6, December 1997 (1997-12), pages 928-934, XP002175907 ISSN: 0026-895X the whole document	53-56
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E	WO 01 16159 A (SMITHKLINE BEECHAM CORP) 8 March 2001 (2001-03-08) page 30; claim 1	57-60

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/31509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL 'Online! AC: AC007104, 23 April 1999 (1999-04-23) STONE ET AL.: "Homo sapiens chromosome 4, 16 unordered pieces" XP002175914 abstract</p>	61-64
E	<p>WO 01 12673 A (MERCK PATENT GMBH ;DUECKER KLAUS (DE)) 22 February 2001 (2001-02-22) Sequence 1, 2 page 39; claim 3</p>	61-64
X	<p>JP 11 032770 A (ASAHI CHEM IND CO LTD) 9 February 1999 (1999-02-09) page 19; claim 7</p>	65-68
X	<p>WO 98 56820 A (ELSHOURBAGY NABIL A ;SMITHKLINE BEECHAM CORP (US); LI XIAOTONG (US) 17 December 1998 (1998-12-17) page 30 -page 31; claims 1,2 the whole document</p>	69-72
A		45-48
X	<p>DATABASE EMBL 'Online! AC: AC010984, 29 September 1999 (1999-09-29) WATERSON R.H.: "Homo sapiens chromosome 2 clone RP11-510C1" XP002175915 abstract</p>	73-76
A	<p>DATABASE EMBL 'Online! AC 008892, 15 July 1998 (1998-07-15) WEINSHANK R. H.: "5-Hydroxytryptamine 1B Receptor(-HT-1B) (Serotonin Receptor)" XP002175948 abstract</p>	73-76
X	<p>MAHAIRAS GREGORY G ET AL: "Sequence-tagged connectors: A sequence approach to mapping and scanning the human genome." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 17, 17 August 1999 (1999-08-17), pages 9739-9744, XP002175909 Aug. 17, 1999 ISSN: 0027-8424 the whole document</p>	77-80
E	<p>WO 01 07606 A (SMITHKLINE BEECHAM PLC) 1 February 2001 (2001-02-01) Sequence 2 page 31; claim 4</p>	77-80

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/31509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 49046 A (TERAO YASUKO ;WATANABE TAKUYA (JP); SHINTANI YASUSHI (JP); TAKEDA) 24 August 2000 (2000-08-24) claim 5; figure 1 -----	77-80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/31509

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4

G protein-coupled receptor as characterized by SEQ.ID.2, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.1, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

2. Claims: 5-8

G protein-coupled receptor as characterized by SEQ.ID.4, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.3, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

3. Claims: 9-12

G protein-coupled receptor as characterized by SEQ.ID.6, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.5, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

4. Claims: 13-16

G protein-coupled receptor as characterized by SEQ.ID.8, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.7, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

5. Claims: 17-20

G protein-coupled receptor as characterized by SEQ.ID.10, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.9, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

6. Claims: 21-24

G protein-coupled receptor as characterized by SEQ.ID.12, its non-endogenous, constitutively activated version SEQ.ID.84, a cDNA encoding said receptor as characterized by SEQ.ID.11, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 25-28

G protein-coupled receptor as characterized by SEQ.ID.14, its non-endogenous, constitutively activated version SEQ.ID.88, a cDNA encoding said receptor as characterized by SEQ.ID.13, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

8. Claims: 29-32

G protein-coupled receptor as characterized by SEQ.ID.16, its non-endogenous, constitutively activated version SEQ.ID.92, a cDNA encoding said receptor as characterized by SEQ.ID.15, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

9. Claims: 33-36

G protein-coupled receptor as characterized by SEQ.ID.18, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.17, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

10. Claims: 37-40

G protein-coupled receptor as characterized by SEQ.ID.20, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.19, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

11. Claims: 41-44

G protein-coupled receptor as characterized by SEQ.ID.22, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.21, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

12. Claims: 45-48

G protein-coupled receptor as characterized by SEQ.ID.24, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.23, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. Claims: 49-52

G protein-coupled receptor as characterized by SEQ.ID.26, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.25, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

14. Claims: 53-56

G protein-coupled receptor as characterized by SEQ.ID.28, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.27, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

15. Claims: 57-60

G protein-coupled receptor as characterized by SEQ.ID.30, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.29, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

16. Claims: 61-64

G protein-coupled receptor as characterized by SEQ.ID.32, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.96, a plasmid comprising said SEQ.ID 95, and a host cell comprising said plasmid.

17. Claims: 65-68

G protein-coupled receptor as characterized by SEQ.ID.34, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.33, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

18. Claims: 69-72

G protein-coupled receptor as characterized by SEQ.ID.36, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.35, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. Claims: 73-76

G protein-coupled receptor as characterized by SEQ.ID.38, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.37, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

20. Claims: 77-80

G protein-coupled receptor as characterized by SEQ.ID.40, its non-endogenous, constitutively activated version, a cDNA encoding said receptor as characterized by SEQ.ID.39, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

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